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CYTYC CORPORATION
250 CAMPUS DRIVE
MARLBOROUGH, MA 01752

EXAMINER	
SANG, HONG	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/622,743
Filing Date: July 21, 2003
Appellant(s): HUNG, DAVID T.

Theodore R. Allen
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 6/5/07 appealing from the Office action mailed 11/17/06.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

8) Evidence Relied Upon

US 6,287,790 B1	Lelièvre et al.	9-2001

Medical News "Breast fluid cells help in early cancer detection", JAMA, 1973, 224(6): 823-827.

Love et al. "Breast-duct endoscopy to study stages of cancerous breast disease", Lancet, 1996, 348(12): 997-999.

Hou et al. "A simple method of duct cannulation and localization for galactography before excision in patients with nipple discharge", Radiology, 1995, 195(2): 568-569.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13, 14, 17, 25, 26 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over JAMA (1973, 224(6): 823-827, IDS) in view of Love et al. (Lancet 1996, 348: 997-999, IDS), Hou et al. (Radiology, 1995, 195 (2): 568-569, IDS) and US Patent No. 6,287,790 B1 (Data of Patent: 9/11/2001, effective filing date 11/30/1998).

Claims are drawn to a method for identifying a patient having breast cancer or breast precancer, said method comprising; placing a ductal access tool comprising a single lumen in a breast duct of a patient; infusing a fluid into the duct through the single lumen; retrieving a ductal fluid sample from the accessed duct through the single lumen; and examining the ductal fluid sample to determine the presence of a marker comprising an expression product of a gene encoding a nuclear matrix protein. Claims are further limited wherein the expression product is a polypeptide, the nuclear matrix protein is nuclear mitotic spindle apparatus protein (NuMA), the fluid collected is from a single duct, a ductal fluid sample is collected from a plurality of ducts, the single lumen has an inner diameter large enough to retrieve clusters of greater than 10 cells.

The JAMA reference teaches a method for early detection of breast cancer comprising inserting a catheter into a breast duct, flushing the duct with saline for cell studies, and examining the fluid from each duct separately (see page 823, left column,

4th paragraph, and page 827, left column, 3rd paragraph). The JAMA reference teaches that the fluid sample contains usable cells (see page 826). The JAMA reference teaches that the fluids are tested for reverse transcriptase, an enzyme that has been implicated as a possible cancer marker (page 827, left column, 5th paragraph).

JAMA reference does not teach that the sample is collected from a plurality of ducts. JAMA reference does not teach detecting NuMA using an antibody. JAMA reference does not teach retrieving a ductal fluid sample from the accessed duct through the lumen of the catheter. JAMA reference does not teach that the lumen has an inner diameter large enough to retrieve clusters of greater than 10 cells. However, these deficiencies are made up for in the teachings of Love, Hou and the US Patent No. 6,287,790 B1.

Love et al. teach a method of collecting ductal fluid from a breast comprising inserting a cannula (0.4 mm outer diameter) into one or more breast ducts, infusing saline into the breast ducts, collecting the washings from the ducts and analyzing the washings cytologically (see page 997, right column under methods). Love et al. teach that the ducts containing DCIS (ductal carcinoma-in-situ) that were successfully cannulated gave rise to exfoliated DCIS cells which could be retrieved by washings; and the cells were confirmed as DCIS cells by positive membrane neu immunoreactivity, positive nuclear p53 immunoreactivity or aneuploidy (see page 999, left column, 1st paragraph). Love et al. teach that breast-duct cannulation and endoscopy can give access to the milk ducts, yield cells that can be analyzed for intermediate markers, and give information about the anatomy of the ductal systems and the pattern of DCIS (page

999, right column, 3rd paragraph). Love et al. disclose that because the duct was so small that is difficult to aspirate back through a cannula to obtain material, the sample was collected externally in a capillary tube after removing the catheter, and this collecting method is not optimal and a double-lumen tube is being developed to overcome this difficulty (see page 998, right column, 2nd paragraph).

Hou et al. teach a simple method of breast duct cannulation and localization, which comprises cannulating a breast duct with a 0.7mm diameter, 1.9 cm long intravenous catheter, infusing a small volume of sterile, water soluble contrast material into the breast duct, and aspirating the contrast solution from the duct through the catheter (see page 568, middle column, last paragraph and right column, 1st paragraph). The catheter used by Hou (0.7 mm diameter) is large enough to retrieve clusters of greater than 10 cells. Hou et al. disclose that galactography and duct cannulation were successfully performed in all 72 patients and no duct was perforated with use of their simple technique (see page 1995, right column, 3rd paragraph). Hou et al. disclose that pathologic evaluation revealed five cases of carcinoma, 37 intraductal papilloma, 14 papillomatosis, six ductal estasia and 10 fibrocystic disease (see page 1995, last paragraph).

US Patent No. 6,287,790 B1 teaches that NuMA can be used to identify tumor cells and different stages in the breast tumor progression and differentiation processes (see abstract). US Patent No. 6,287,790 B1 teaches that proliferating non-malignant and malignant mammary epithelial cells show significantly different nuclear distribution

of NuMA protein (see Fig. 11). US Patent No. 6,287,790 B1 teaches detection of NuMA using a NuMA specific antibody (see abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of JAMA and/or Love to use the catheter of Hou to retrieve ductal fluid and further detect the NuMA expressed on ductal cancerous epithelial cells for breast cancer diagnosis. One would have been motivated to do so because Love teaches that collecting ductal fluid externally after removing the catheter is not optimal, and other methods such as using double-lumen tube is developed to overcome this difficulty. One skilled in the art would recognize that infusing the washing solution and aspirating the washings through the lumen of the catheter is a simpler, and more effective method to retrieve ductal fluid. Moreover, because Hou's method can provide ductal fluid that is free of contamination of the fluids coming from other ducts, specific diagnosis can be made to each breast duct. One skilled in the art would have been motivated to detect NuMA on ductal epithelia cells for identifying cancerous cells because Patent ' 790 teaches that NuMA is a breast cancer marker that can be used to identify breast tumor cells and different stages in the breast tumor progression and differentiation processes. One of ordinary skill in the art would have a reasonable expectation of success to do so because JAMA and Love teach methods of diagnosis of breast cancer comprising collecting ductal fluid by ductal lavage, and further detecting breast cancer markers expressed on ductal cancerous cells, Hou teaches a method of breast duct cannulation comprising cannulating a breast duct with a catheter, infusing a solution into the duct and aspirating the solution from the

duct through the catheter and Patent' 790 teaches a method of detecting NuMA in breast epithelial cells using a NuMA specific antibody.

(10) Response to Argument

Appellants presented the following arguments, each of them is responded below.

A. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

The Brief states that Love describes a method of using endoscopy to study stages of cancerous breast disease. Hou teaches a method of duct cannulation for galactography before excision of a patient's breast. Hou does not teach or suggest the use of a single lumen catheter to introduce and remove wash fluid from a breast duct for the purpose of analyzing the contents of the wash solution. It is difficult to imagine that one skilled in the art would look to Hou to overcome the technical difficulties of Love. First, although both Hou and Love use the same technical procedure of cannulating a breast duct, Hou was not concerned with the removal of fluid from the breast duct for the analysis of cancer markers. Hou merely describes the removal of fluid containing contrast agent from a breast duct after the successful completion of a mammogram. Second, the Examiner has not pointed out with any specificity to any teaching or suggestion in Hou that overcomes Love's technical difficulties. There is no discussion in Hou of any change or modification of the methodology to overcome a technical difficulty. The Appellants respectfully submits that the Examiner has, at most,

set forth an "obvious to try" rationale in support of this obviousness rejection. However, an "obvious to try" rationale is not the appropriate standard for obviousness under 35 U.S.C. §103 (M.P.E.P. §2145).

Appellant's arguments have been carefully considered but are not persuasive. Both Sartorius (see page 823, left column, 4th paragraph, and page 827, left column, 3rd and 5th paragraphs) and Love (see page 997, right column under methods) teach use of a catheter to introduce a wash fluid to a breast duct, collecting washings from the ducts, analyzing the washings and determining the presence of cancer cells or precancerous cells by detecting markers such as reverse transcriptase, positive membrane neu immunoreactivity, positive nuclear p53 immunoreactivity or aneuploidy. The motivation to modify the method of Sartorius and/or Love to use the catheter of Hou to retrieve ductal fluid comes from the teachings of Love and the knowledge generally available to one of ordinary skill in the art. Love et al. disclose that because the duct was so small that is difficult to aspirate back through a cannula to obtain material, the sample was collected externally in a capillary tube after removing the catheter, and this collecting method is not optimal and a double-lumen tube is being developed to overcome this difficulty (see page 998, right column, 2nd paragraph). Therefore, Love clearly pointed out that collecting the fluid externally after removing the catheter is not optimal, and indicated that a method of retrieving ductal fluid in situ using a double-lumen tube is being developed. One skilled in the art would recognize that infusing the washing solution and aspirating the washings through the same catheter (i.e. Hou's method) is a better method than collecting the ductal fluid externally in a capillary tube after removing

the catheter (Love's method). First, given the fact that only a small volume of wash solution can be infused to a single breast duct (about 0.2-0.5ml, see Love's reference page 997, right column, 4th paragraph), Hou's method (the catheter stays in the duct during infusing and aspirating), would be expected to collect or recover more ductal washings than Love's method where the small amount of washings must flow all the way to the nipple. Second, because Hou's method can provide ductal fluid that is free of contamination of the fluids coming from other ducts, specific diagnosis can be made to each breast duct. By using a catheter that has a diameter (0.7 mm) bigger than the one of Love used (0.4mm), Hou et al. successfully performed galactography and duct cannulation in all 72 patients and no duct was perforated with use of their simple technique (see page 1995, right column, 3rd paragraph). While the method of Hou is not for the purpose of analyzing the contents of the wash solution, it does provide a solution for Love's problems. A prior art reference is analogous if the reference is in the field of applicant's endeavor or, if not, the reference is reasonably pertinent to the particular problem with which the inventor was concerned. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). In the instant case, both Love's reference and Hou's reference are in the same filed of appellant's endeavor, i.e. breast cancer diagnosis, and both use the same technique i.e. breast duct cannulation. Therefore, in view of the teachings of Hou et al., one skilled in the art would have been motivated to modify the method of Love.

B. There is no reasonable expectation of success

The Brief states that Love clearly demonstrates the difficulty of using a single lumen catheter to aspirate ductal fluid from a breast duct, and the authors suggested that a double lumen catheter to overcome the problems; however, there is nothing in Love that would teach one of skill in the art that such a modification would overcome the technical problem. The Brief states that the Examiner's argument that the teachings of Love suggest that retrieving the ductal washings through a lumen is a preferred method to collecting the washings externally is not supported by the evidence and the use of a single lumen catheter is clearly unsupported by the teaching of Love. Hou does not overcome the deficiencies of Love because the use of a single lumen catheter in Hou does not address the technical problems that Love encountered. The Examiner has not provided any argument of why the single lumen catheter that did not work in Love could be successfully substituted by the single lumen catheter in Hou.

Appellant's arguments have been carefully considered but are not persuasive. The reasons why one skilled in the art would recognize that retrieving the washings through a lumen is a preferred method to collecting the washings externally have been set forth above (see A). By using a catheter that has a diameter (0.7 mm) bigger than the one of Love used (0.4mm), Hou et al. successfully performed galactography and duct cannulation in all 72 patients and no duct was perforated with use of their simple technique (see page 1995, right column, 3rd paragraph). Because Sartorius and Love teach a method for diagnosing breast cancer comprising isolating ductal fluid by ductal lavage, and further detecting ductal cancerous epithelial cells and cancer marker, Hou

has successfully cannulated the breast duct and retrieved the solutions through the lumen of the catheter, one of ordinary skill in the art would have a reasonable expectation of success to use the catheter of Hou's to retrieve ductal washings through the lumen for cancer detection.

C. The prior art reference (or combined references) does not teach or suggest all the claim limitation.

The Brief states that neither Sartorius nor Love teach or suggest a method of introducing and retrieving a sample from a breast duct via a single lumen catheter. Hou does not teach or suggest the introduction and retrieval of a ductal lavage solution from a duct through a catheter. Hou teaches a method for introducing a dye into a breast duct solely for the purpose of galactography. There is nothing in Hou that teaches or suggests that the dye removed from the duct after the procedure is over contains any cellular material or markers that would be useful in detecting cancer or precancer. The Brief states that neither Sartorius nor Love teach or suggest detecting the presence of a cancer marker in the isolated ductal fluid. The "marker" used in Sartorius is not used to determine the presence of cancer in a patient. Sartorius is at best ambiguous as to whether or not the presence of high amounts of reverse transcriptase is a cancer marker in breast ductal fluid. Love uses positive membrane neu immunoreactivity, positive nuclear p53 immunoreactivity or aneuploidy to confirm a previous diagnosis of DCIS, not to identify a patient having breast cancer or breast precancer. The Brief states that Lelievre does not teach or suggest that NuMA is a breast cancer marker that

can be used to identifying a patient having breast cancer or breast precancer. Lelievre teaches the use of NuMA as a marker for examining the different stages in the breast tumor progression.

Appellant's arguments have been carefully considered but are not persuasive because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Both Sartorius (see page 823, left column, 4th paragraph, and page 827, left column, 3rd and 5th paragraphs) and Love (see page 997, right column under methods) teach use of a catheter to introduce a wash fluid to a breast duct, collecting washings from the ducts, analyzing the washings and determining the presence of cancer cells or precancerous cells by detecting markers such as reverse transcriptase, positive membrane neu immunoreactivity, positive nuclear p53 immunoreactivity or aneuploidy. While neither Sartorius nor Love teach retrieving ductal wash fluid from the accessed duct through lumen of the catheter, these deficiencies are made up for in the teaching of Hou. Hou teaches a method of infusing a small volume of sterile, water soluble contrast material into the breast duct, and aspirating the contrast solution from the duct through the catheter (see page 568, middle column, last paragraph and right column, 1st paragraph). Regarding detecting cancer markers in ductal fluid, Love et al. teach that the ducts containing DCIS (ductal carcinoma-in-situ) that were successfully cannulated gave rise to exfoliated DCIS cells which could be retrieved by washings; and the cells were confirmed as DCIS cells by positive membrane neu immunoreactivity, positive

nuclear p53 immunoreactivity or aneuploidy (see page 999, left column, 1st paragraph). Therefore, Love teaches the method step of examining the ductal fluid sample to determine the presence of a marker. Love et al. further teach that breast-duct cannulation and endoscopy can give access to the milk ducts, yield cells that can be analyzed for intermediate markers, and give information about the anatomy of the ductal systems and the pattern of DCIS (page 999, right column, 3rd paragraph). While Neither Sartorius nor Love teach detection of NuMA in the ductal fluid, in view of the teachings of Lelievre that NuMA can be used to identify tumor cells and different stages in the breast tumor progression and differentiation process (see abstract), and proliferating non-malignant and malignant mammary epithelial cells show significantly different nuclear distribution of NuMA protein (see Figure 11), and further in view the teaching of Love that cancer epithelial cells are present in the ductal wash fluid, one skilled in the art would have been motivated to modify the method of Sartorius and/or Love to detect NuMA in the ductal fluid for diagnosis of breast cancer. Therefore, the combination of the references teach every limitation of the claims.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Hong Sang, Ph.D.

Art Unit 1643 Hong Sang

Oct. 5, 2007

Conferees:

Larry R. Helms

/Larry R. Helms/

Supervisory Patent Examiner

/Robert A. Wax/

TQAS Appeals Specialist

TC 1600